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DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation Study in Rats TOX. CHEM. NO.: 838B

MRID NUMBER: 401413-02

TEST MATERIAL: Tefluthrin, technical

SYNONYMS: ISO-provisional name: PP993

STUDY NUMBER: CTL Study No. HR0611

SPONSOR: ICI AMERICAS INC.

TESTING FACILITY: Imperial Chemical Industries PLC-Central Toxicology Laboratory

TITLE OF REPORT: Tefluthrin: 4 Hour Acute Inhalation Toxicity Study in the Rat

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CONCLUSIONS: The approximate four-hour median lethal concentration of technical tefluthrin is 37.1 mg/m^3 for females and 49.1 mg/m^3 for males (overall-42.7 mg/m^3). The neurotoxic effects seen were considered to be typical of those observed following exposure to a synthetic pyrethroid; the NOEL for toxic effects was said to be 7.7 mg/m^3.

Classification: minimum

QUALITY ASSURANCE: A quality assurance statement was provided.

A. METHODS AND MATERIALS:

1. Test Compound: Tefluthrin technical Description: white powder, Batch No.: P18, Purity: 96.0%.

2. Test Animals: Species: Rat, Strain: SPF, Alpk: AP (Wistar-derived) albino, Age: 7 week on arrival (6/7-day acclimatization), Weight: males 216-237 grams and females 195-223 grams for the control, low-, and 2 mid-dose groups; males 221-257 grams and females 204-237 grams for the high-dose group, Source: Alderley Park, Cheshire, UK.

3. Statistics: Test and control data were compared using a two-sided Student's t-test. Linear log dose interpolation was used to provide an estimate of the median lethal concentration for males. An estimate of the LC_{50} for females and for the overall mortality of both sexes was obtained using the method of Spearman-Karber[1].

B. STUDY DESIGN:

1. Exposure: Animals (5 rats/sex/group) were to be exposed for a single period of up to four hours via inhalation, to aerosols with a target particle size of $\leq$ 2.5 um AED at target tefluthrin concentrations of 0, 5, 20, 50, or 65 mg/m^3 (solutions in ethanol) and were then maintained untreated for a 14-day observation period. The controls were exposed to air only, but were treated in a similar manner. The animals were exposed nose-only in restraining tubes, which were inserted into an exposure chamber.

   Note: The high-dose group was exposed to the test material one day after the other groups were exposed. The high-dose exposure was terminated after 198 minutes because of the severe toxic response elicited in these animals.

2. Observations: The animals were observed frequently during exposure and, at the end of exposure, each rat was given a detailed clinical examination (see Appendix 5) for signs of toxicity and mortality. Body weights were recorded on day -1, the day of exposure, and on days 2-8 and 15 of the observation period. Food consumption per cage (5/sex/cage) was measured daily between days -1 to 15.

3. Gross Pathology: Each animal was subjected to a gross macroscopic examination, with particular attention being given to abdominal and thoracic viscera. Lungs (with trachea attached but larynx removed), liver, kidneys, and testes were weighed (paired organs were weighed together). The following tissues were examined: head (for nasal turbinates), lungs, larynx, trachea, liver, kidneys, ovaries, testes, and any abnormal tissue.

C. RESULTS:

1. Dose

   The physical characteristics of the test material posed no problems in the generation of aerosols at target particulate concentrations of 5, 20, 50, or 65 mg tefluthrin/m^3. The achieved mean analyzed concentrations of 7.7, 14.9, 39.9, and 60.5 mg/m^3 tefluthrin accounted for greater than 80% of the total particulate. The three high dose levels were reported to have a respirable ($\leq$ 2.5 um AED) content greater than 90% and a mass median aerodynamic diameter (D_{50}) of approximately 1.3 um. The analyzed and particulate aerodynamic particle size distributions for all dose levels were reported to show a good correlation at respirable levels, and the authors concluded that the atmosphere concentrations achieved provided an adequate basis for assessing the acute inhalation toxicity of tefluthrin (see Atmosphere Analysis, pages 10-12, appended).

2. Clinical Observations

Survival

There were no deaths reported in the control or test animals of the 20 mg/m^3 and 5 mg/m^3 groups during this study. All high-dose (65 mg/m^3) animals died or were killed in extremis on day 1 (one female died during exposure, 3 males and 3 females died shortly after exposure, and the remaining 2 males and 1 female were killed in extremis shortly thereafter). Two 50 mg/m^3 females were killed in extremis after exposure on day 1. The remaining 8 animals in this group survived to termination.

Clinical Signs

Abnormalities generally associated with restraint (stains around snout, wet fur) were reported in all groups. All test material animals were noted to salivate during exposure, but the two high-dose groups were said to have displayed this effect sooner and more severely than the other groups (see Table 4, attached). After 175 minutes of exposure, all top-dose (65 mg/m^3) animals appeared agitated and 2 had blood around the face. Exposure of this group was terminated at 198 minutes.

All animals were said to have displayed clinical effects generally associated with restraint (hunched posture, piloerection, stains around nose, and wet fur) immediately following exposure. Other effects were said to be dose-related in severity and number of animals affected. The 8 top-dose animals still alive following exposure displayed tonic convulsions and gasping.

In general, the clinical signs noted were more severe and lasted longer in the higher doses compared to the low and control groups. Survivors showed a rapid reversal of symptoms after cessation of exposure (see Tables 4 and 5, attached).

Body Weights and Food Consumption

Mean body weight of all surviving groups was reduced following exposure. This was reported as not dose-related; the greatest effect was observed in the 50 mg/m^3 female group. The low- and mid-dose animals had body weight patterns that were comparable to control.

The weight gain of the high-dose (50 mg/m^3) males was reported as similar to control, but the overall weight gain was slightly lower ($p < 0.05$ was not attained). The high-dose (50 mg/m^3) females did not exceed their starting weight until day 4, and the low-dose females displayed as erratic weight pattern up to day 5. Thereafter, the weight pattern in the female test groups was reportedly similar to control.

There was a slight decrease in food consumption following exposure on days 1 and 2 in the 50 mg/m^3 animals and in the 20 mg/m^3 females compared to control. After day 2, the females test groups were similar to controls. the high-dose males showed a slightly lower intake towards the end of the study compared to controls, which corresponded to a slight reduction in weight.

3. Gross Pathology

Organ Weights

Relative kidney weights were increased (dose-related) in the 20 mg/m^3 and 50 mg/m^3 dose groups, although the effects was noted to be small (8% in the high-dose). The 65 mg/m^3 males that were killed *in extremis* were not compared statistically to the concurrent controls, but their relative kidney weight was said to be increased for animals of this age. A similar finding was reported for the 50 mg/m^3 and 65 mg/m^3 females killed *in extremis* on day 1. The relative lung weight of the highest dose group (non-survivors) was also higher than normal for this age. The relative testes weight was reported to be increased in the 50 mg/m^3 group, but the authors considered this small increase (10%) to be a reflection of the slightly lower body-weight gain in this group compared to control (see Tables 8 and 9, attached).

Macroscopic Examination

No treatment-related effects were reported in the animals that survived to day 15. Abnormalities attributable to treatment were reported in high-dose animals only, all of which died or were killed *in extremis* on day 1 (see Table 10).

DISCUSSION:

No solvent control was used; however, the authors stated that ethanol was not expected to cause any acute additive or synergistic effect since the 4-hour median lethal concentration of ethanol is in excess of 45,000 ppm and light narcosis is the main effect observed at atmosphere concentrations of 20,000-23,000 ppm. The concentrations of ethanol reached in this study did not exceed 7000 ppm.

Severe toxic effects were observed at the highest dose level tested (65 mg/m^3). Animals in the three highest dose levels (20, 50, 65 mg/m^3) showed dose-related (in severity and number of animals affected) symptoms of neurotoxicity considered typical of those associated with exposure to synthetic pyrethoids. The lowest dose (5 mg/m^3) did not produce these symptoms. Survivors showed a rapid reversal of the neurotoxic symptoms following cessation of exposure, another typical feature of the response to a compound of this type.

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